Remarks/Arguments

I. Specification

The Office Action advises that the sequences in Figure 1 be identified by SEQ ID numbers and must comply with the Sequence Rules. Applicant has taken the advice and amended the description of Figure 1 (See page 2 of this paper).

II. Claim Rejections under 35 U.S.C. 112

A. Rejections of claims 23-41, 43, 48, 50-54, 63, 73-74, 81-82, 85 and 141-142.

The Office Action rejects claims 23-41, 43, 48, 50-54, 63, 73-74, 81-82, 85 and 141-142 under 35 U.S.C. 112, second paragraph, for being indefinite for failing to particularly point our and distinctly claim the subject matter which Applicant regards as the invention. In particular, the Office Action asserts that it is unclear what the second cell is comprised of.

To the extent that the rejections may be applied to the amended claims, Applicant respectfully traverses. Under the current amendment, the second cell is a cell that does not contain the altered mammalian enzyme but is otherwise substantially identical or similar to the first cell. The support for the amendment can be found at, for example, page 14, lines 25 – 30, in the specification.

Since the second cell is clearly defined, Applicants respectfully requests that the rejections be reconsidered and withdrawn.

B. Rejections of claims 23-41, 43, 48, 50-54, 63, 73-74, 81-82, 85 and 141-142.

The Office Action rejects claims 23-41, 43, 48, 50-54, 63, 73-74, 81-82, 85 and 141-142 under 35 U.S.C. 112, second paragraph, for being incomplete for omitting essential elements. In particular, the Office Action asserts that what is comprised in the "conditions that inhibit" the enzyme is an omitted element.

To the extent that the rejections can be applied to the amended claims, Applicant respectfully traverses. The term "conditions" is clearly defined in the specification. The "conditions" are what cells may be exposed or subjected to which include, but are not limited to, environmental factors, such as, for example, temperature, light, pH, radiation and pressure; chemical compositions or agents, such as, for example, drugs, enzyme inhibitors, chemotherapeutic agents and antibiotics; and combination thereof. See, p. 32, ll. 27-31, in the specification. In one embodiment of the invention, conditions which inhibit unaltered forms of mammalian enzymes are selection agents under which cell containing a selectable marker (e.g. an altered form of a mammalian enzyme) will exhibit greater proliferation and/or viability than at least substantially identical cell that do not contain the altered enzyme. P. 5, ll. 18 – 21 & ll. 9-13. The selection agents include, but are not limited to, drugs, substances used as chemotherapeutic agents, biosynthetic enzyme inhibitors, enzymes that degrade and/or inactivate toxic agents,

antibiotics, and antibodies. P. 103. ll. 25-28. In one embodiment wherein a selection agent is an inhibitor to a mammalian enzyme, the condition which inhibits unaltered forms of the enzyme is such that at least certain cells exposed to the inhibitor exhibit reduced proliferation and/or viability relative to the amount of proliferation and/or viability of the cells in the absence of the inhibitor. P. 5, ll.18 – 24.

In sum, what is comprised in the "conditions that inhibit" is clearly defined in the specification. Accordingly, Applicant respectfully requests that the rejections be reconsidered and withdrawn.

C. Rejections of claims 23-41, 43, 48, 50-54, 63, 73-74, 81-82, 85 and 141-142.

The Office Action rejects claims 23-41, 43, 48, 50-54, 63, 73-74, 81-82, 85 and 141-142 under 35 U.S.C. 112, second paragraph, for being incomplete for omitting essential steps. In particular, the Office Action asserts that the omitted steps include how the inhibitors are contacted with the enzyme and how the compositions of claims 41 are exposed to the cells.

Applicant respectfully traverses. Applicant specifically teaches that cells containing the DNA encoding an altered enzyme can be cultured in the presence of an inhibitor. P. 59, ll. 16-20, p. 70, ll. 25-28. Applicant further teaches that for selective proliferation and /or viability *in vivo* an inhibitor can be administered to an organism. P. 27, ll. 20-23, p. 109, ll. 3-4, p. 109, ll. 8-16.

With respect to claim 41, the compositions of claim 41 are exposed to cells by culturing the cells with the composition (p. 101, ll. 15-17) or contacting cells with

antigens, monoclonal antibodies, cytokines, growth factors, mitogens and combinations thereof (P. 102, ll. 3-5). An illustrative example is to culture the cells *in vitro* with the compositions. (p. 102, ll. 5-10).

In light of the foregoing, Applicant believes that no essential steps are omitted in the claims. Accordingly, Applicant respectfully requests that the rejections be reconsidered and withdrawn.

D. Rejections of claims 73-74 and 142-143.

The Office Action rejects claims 73-74 and 142-143 asserting that the exact location of the specific amino acid can be confusing. However, the Office Action states that the rejection can be overcome by amending the claims as "amino aid position".

Applicant has amended the claims in accordance with the Office Action's suggestion. Accordingly, Applicant respectfully requests that the rejections be withdrawn.

F. Rejections of claims 74 and 143.

The Office Action rejects claims 74 and 142 asserting that it is not clear whether the claims comprise three or two clauses and where the nucleotides TCGAGG is located.

Applicant has amended the claims to be directed to three clauses. In addition, the nucleotides TCGAGG is located at the nucleotide residues from # 614 to #619 in

SEQ. ID. NO. 3, as shown in the amended claims. Accordingly, Applicant respectfully requests that the rejections be withdrawn.

III. Claim Rejections under 35 U.S.C. 103

The Office Action rejects claims 23-41, 43, 48, 50-54, 63, 73-74, 81-82, 85 and 141-142 under 35 U.S.C. 103(a) as being unpatentable over Farazi et al., in view of Krysteck et al., in further view of the Stratagene Catalog. To the extent that the rejections can be applied to the amended claims, Applicant respectfully traverses.

It is long established that to establish a *prima facie* case of obviousness three basic criteria must be met. First, there must be some suggestion or motivation to modify or combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Farazi et al teach that inhibitors of inosine-5'-monophosphate dehydrogenases (IMPDH) have anti-proliferative activity (p. 961). Given that most microbial IMPDHs are not sensitive to mycophenolic acid (MPA) which is a potent and specific inhibitor of mammalian IMPDHs (Abstract), Farazi et al suggest that differences in the properties of microbial and mammalian IMPDHs present an opportunity to design species-selective IMPDH inhibitors that will be useful for anti-infective chemotherapy (P. 961). It is commonly known in the art that anti-infective activity is anti-proliferative to microbes. Farazi et al. further teach some specific MPA-resistant mutants of human IMPDH.

Accordingly to Farazi et al., these mutations occur in the regions of the human IMPDH that are different from microbial IMPDHs and are possibly structure determinants of MPA selectivity (Abstract). However, Farazi et al. do not teach selective proliferation and/or viability of the first cell into which a nucleic acid encoding an altered mammalian enzyme resistant to conditions inhibiting the unaltered enzyme is introduced over the second cell that does not contain the altered enzyme.

Krysteck et al. teach that IMPDH is important for diseases involving proliferation of B and T lymphocytes or viral diseases (col. 1, para 0006) and thus inhibitors that inhibit the activity of a wild type IMPDH may be useful to treat the diseases (para 0011). Krysteck et al. further teach a modified human IMPDH that is modified to include a substitute oligo-peptide replacing a subdomain region of the wild type IMPDH (para 0012). The modified IMPDH is shorter than its wild type counterpart and confers a finer resolution in the crystal structure (para 0012). In particular, Krysteck et al. teach that the modified IMPDH exhibits the functional activity of the wild type IMPDH in that the modified IMPDH is inhibited by compounds known to inhibit the activity of wild-type IMPDH (para 0109). Therefore, Krystek et al do not teach a modified mammalian enzyme that is resistant to conditions that inhibit the unaltered enzyme (the wild-type), much less selective proliferation and/or viability of a first cell into which a nucleic acid encoding an altered mammalian enzyme is introduced over a second cell that does not contained the altered enzyme.

The Stratagene Catalog provides a cell proliferation assay kit known as "Quantos™ Cell Proliferation Assay Kit". The kit is used to quickly and accurately

quantitate the number of cell at the range typically found in tissue culture. However, the kit does not teach how to proliferate cells, much less selective proliferation and/or viability of a first cell into which a nucleic acid encoding an altered mammalian enzyme is introduced over a second cell that does not contain the altered enzyme.

In light of the foregoing, it appears that none of the above-cited references teach the claimed method for selective proliferation and/or viability of a first cell into which a nucleic acid encoding an altered mammalian enzyme is introduced over a second cell that does not contain the altered enzyme. Accordingly, the references when combined do not teach or suggest all limitations of the claimed invention.

Applicant further notes that there is no suggestion or motivation to combine the references together. It is well established that the factual inquiry into motivation to modify or combine reference "could not be resolved on subjective belief and unknown authority" but "must be based on objective evidence of record." *In re Sang Su Lee*, 277 F.3d 1338 (Fed. Cir. 2002). It is improper in determining whether a person of ordinary skill in the art would have been led to this combination of references simply to use that which the inventor taught against it teacher. Id.

The Office Action asserts that "it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use the mutant of Farazi et al, or to make similar mutant using the wild type IMPDH taught by Krysteck et al. and screen whether the mutants have resistance against inhibitors of IMPDH by performing cell proliferation assays, comparing cells containing the mutant enzymes

and cell containing wild-type IMPDH". In inquiring into motivation, the Office Action states that the "motivation of performing the cell proliferation assay is to determine if the mutant IMPDH are resistant to IMPDH inhibitors since the inhibition of IMPDH results in anti-proliferative activity" and "IMPDHs that are resistant to its inhibitors can be useful in anti-infective chemotherapy by designing species-selective IMPDH inhibitors".

Applicant has pointed out that Krysteck et al. only teach mutant IMPDHs that are inhibited by inhibitors to wild-type IMPDH, not resistant to the inhibitors. Applicant has also pointed out that the Stratagene's proliferation assay merely measures the number of cells without teaching any methods as to how to proliferate cells. The Office Action has not explained how the Stratagene's assay can be used to determine whether a mutant IMPDH is resistant to IMPDH inhibitors, nor has it expalined how the Stratagene's assay teaches methods for selective proliferation and/or viability of cells which are taught by Applicant in the present invention..

In addition, the references appear to teach away from the claimed invention. The IMPDH mutants taught by Krysteck et al. are not resistant to the inhibitor at all and are used to attain a fine crystal structure of IMPDH. The IMPDH mutants taught by Farazi et al are used to understand the structural determinants for various MPA sensitivity among various species so that species-selective IMPDH inhibitors can be designed for anti-infective chemotherapy. In other words, the IMPDH mutants taught in the art are directed to understanding a better crystal structure of IMPDH or identifying better IMPDH inhibitors for anti-proliferative activity or anti-infective activity. The anti-infective activity by its nature is anti-proliferative to microbes. It follows that the

references discourage a skilled artisan to use IMPDH mutants and selectively proliferate or vitalize cells into which a nucleic acid encoding an altered mammalian enzyme resistant to inhibition is introduced over cells that do not contain the altered enzyme. It is one thing that IMPDHs resistant to their inhibitor s can be useful in anti-infective chemotherapy. It is quite an opposite that mutant mammalian enzyme resistatn to their inhibitors can be used in proferating and/or titalizing cells to which a nucleic acid encoding an altered mammalian enzyme resistant to inhibition is introduced.

Unless the Office Action can fulfill its obligation by citing objective evidence of record to support the motivation rather than using the teaching of the present invention at hindsight, Applicant finds no support for teaching or motivation to combine the references, not to mention that the hypothetical combination does not render the claimed invention since the combination does not teach all limitations of the claimed invention.

In light of the above, Applicant respectfully requests that the rejections of claims 23-41, 43, 48, 50-54, 63, 73-74, 81-82, 85 and 141-142 under 35 U.S.C. 103(a) be reconsidered and withdrawn.

Applicant believes that the present amendment places the application in condition for allowance. A Notice of Allowance is, therefore, respectfully requested. If any additional issue needs to be addressed to expedite the prosecution of this application, please feel free to call the undersigned at (310) 788-3218.

Respectfully submitted,
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